



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> :  C12Q 1/68		A3	(11) International Publication Number: <b>WO 00/42216</b>	
			(43) International Publication Date: 20 July 2000 (20.07.00)	
<p>(21) International Application Number: PCT/EP00/00319</p> <p>(22) International Filing Date: 17 January 2000 (17.01.00)</p> <p>(30) Priority Data: 9901037.3 18 January 1999 (18.01.99) GB 9912585.8 28 May 1999 (28.05.99) GB</p> <p>(71) Applicant (<i>for all designated States except US</i>): OSTEOMETER BIOTECH A/S [DK/DK]; OsteoPark, Herlev Hovedgade 207, DK-2730 Herlev (DK).</p> <p>(72) Inventor; and</p> <p>(75) Inventor/Applicant (<i>for US only</i>): KUSK, Philip [DK/DK]; OsteoPark, Herlev Hovedgade 207, DK-2730 Herlev (DK).</p> <p>(74) Agent: SMART, Peter, J.; W.H. Beck, Greener &amp; Co., 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB).</p>			<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 2 November 2000 (02.11.00)</p>	

(54) Title: GENETIC PREDISPOSITION TO ABNORMAL CALCIFICATION CONDITIONS

(57) Abstract

Methods of assessing an individual's predisposition to abnormal calcification conditions such as osteoporosis by determining the genotype of a promoter for the bone sialoprotein gene, the matrix gla protein gene, the osteopontin gene or the osteoprotegerin gene individually or in any combination. Specific allelic variations for each promoter are described.

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# INTERNATIONAL SEARCH REPORT

Inter Application No  
PCT/EP 00/00319

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 C12Q/68

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 97 03555 A (HIROKAWA KATSUIKU ;HOECHST JAPAN (JP); TADA NORIHIRO (JP); IKEDA T) 6 February 1997 (1997-02-06)</p> <p>abstract</p> <p>---</p> <p>EP 0 705 842 A (HOECHST AG) 10 April 1996 (1996-04-10)</p> <p>the whole document</p> <p>---</p> <p>---</p>	<p>1-4, 12, 14-16, 20, 21, 23, 24</p> <p>1-4, 12, 14-16, 20, 21, 23, 24</p>
A		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

14 July 2000

31/07/2000

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

Intelli [REDACTED] Application No  
PCT/EP 00/00319

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIM R H ET AL: "Identification of a vitamin D3-response element that overlaps a unique inverted TATA box in the rat bone sialoprotein gene." BIOCHEMICAL JOURNAL, (1996 AUG 15) 318 (PT 1) 219-26. , XP002142619 the whole document ---	1-3, 7-10, 14-18, 23,24
A	MUNROE P B ET AL: "Mutations in the gene encoding the human matrix Gla protein cause Keutel syndrome." NATURE GENETICS, (1999 JAN) 21 (1) 142-4. , XP000929109 the whole document ---	1-3,5, 11, 14-16, 19,23,24
A	LUO: "Spontaneous calcification of arteries and cartilage in mice lacking GLA protein" NATURE, vol. 386, 6 March 1996 (1996-03-06), pages 78-81, XP002142620 cited in the application the whole document ---	1-3,5, 11, 14-16, 19,23,24
A	EP 0 784 093 A (AMGEN INC) 16 July 1997 (1997-07-16)  the whole document ---	1-3,7, 13-16, 22-24
A	BUCAY N ET AL: "osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification" GENES AND DEVELOPMENT, US, COLD SPRING HARBOR LABORATORY PRESS, NEW YORK, vol. 12, no. 9, 1 May 1998 (1998-05-01), pages 1260-1268, XP002090118 ISSN: 0890-9369 cited in the application the whole document ---	1-3,7, 13-16, 22-24
P,X	BRANDSTROM, H. (1) ET AL: "Polymorphism in the promoter region of the human gene for osteoprotegerin: Correlation with bone mineral density." JOURNAL OF BONE AND MINERAL RESEARCH, (SEPT., 1999) VOL. 14, NO. SUPPL. 1 PP. S334. MEETING INFO.: TWENTY-FIRST ANNUAL MEETING OF THE AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH ST. LOUIS, MISSOURI, USA SEPTEMBER 30-OCTOBER 4 1999 AMERICAN SOCIETY, XP000915449 abstract -----	1-3,7, 13-16, 22-24

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Inter Application No

PCT/EP 00/00319

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9703555	A	06-02-1997	JP	9028235 A		04-02-1997
EP 0705842	A	10-04-1996	AU	695117 B		06-08-1998
			AU	3308695 A		18-04-1996
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			AU	1468697 A		17-07-1997
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			CZ	9702538 A		17-03-1999
			DE	19654610 A		26-06-1997
			EP	0870023 A		14-10-1998
			FR	2742767 A		27-06-1997
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			NO	973699 A		21-10-1997
			NZ	326579 A		28-01-1999
			PL	321938 A		05-01-1998
			SK	110797 A		12-07-1999
			TR	970550 A		21-07-1997
			WO	9723614 A		03-07-1997
			US	6015938 A		18-01-2000

# PATENT COOPERATION TREATY



From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

## NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

Date of mailing (day/month/year)	09.04.2001
-------------------------------------	------------

Applicant's or agent's file reference  
PJS/P7850WO

### IMPORTANT NOTIFICATION

International application No. PCT/EP00/00319	International filing date (day/month/year) 17/01/2000	Priority date (day/month/year) 18/01/1999
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Applicant  
OSTEOMETER BIOTECH A/S

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**  
**(PCT Article 36 and Rule 70)**

Applicant's or agent's file reference  PJS/P7850WO	<b>FOR FURTHER ACTION</b>	
See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)		
International application No.  PCT/EP00/00319	International filing date (day/month/year)  17/01/2000	Priority date (day/month/year)  18/01/1999
International Patent Classification (IPC) or national classification and IPC  C12Q1/68		
<p>Applicant  OSTEOMETER BIOTECH A/S</p>		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I    <input checked="" type="checkbox"/> Basis of the report</li> <li>II   <input type="checkbox"/> Priority</li> <li>III   <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV   <input type="checkbox"/> Lack of unity of invention</li> <li>V   <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI   <input type="checkbox"/> Certain documents cited</li> <li>VII   <input checked="" type="checkbox"/> Certain defects in the international application</li> <li>VIII   <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand  11/08/2000	Date of completion of this report  09.04.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Weijland, A  Telephone No. +49 89 2399 7490



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/00319

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):  
**Description, pages:**

1-48                   as originally filed

**Claims, No.:**

1-24                   as originally filed

**Drawings, sheets:**

1/13-13/13           as originally filed

**Sequence listing part of the description, pages:**

52-55, filed with the letter of 27.03.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/00319

- the description,      pages:  
 the claims,      Nos.:  
 the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.  
 claims Nos. 23,24 (with respect to industrial applicability).

because:

- the said international application, or the said claims Nos. 23,24 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.  
 no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.  
 the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/00319

**1. Statement**

Novelty (N)	Yes:	Claims 1-15, 17-24
	No:	Claims 16
Inventive step (IS)	Yes:	Claims 4-13, 17-22
	No:	Claims 1-3, 14-16, 23, 24
Industrial applicability (IA)	Yes:	Claims 1-22
	No:	Claims

**2. Citations and explanations**  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/00319

The following documents (D) are referred to in this report; the numbering will be adhered to the rest of the procedure:

- D1: KIM R H ET AL: 'Identification of a vitamin D3-response element that overlaps a unique inverted TATA box in the rat bone sialoprotein gene.' BIOCHEMICAL JOURNAL, (1996 AUG 15) 318 (PT 1) 219-226.
- D2: MUNROE P B ET AL: 'Mutations in the gene encoding the human matrix Gla protein cause Keutel syndrome.' NATURE GENETICS, (1999 JAN) 21 (1) 142-144.
- D3: BUCAY N ET AL: 'osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification' GENES AND DEVELOPMENT, US, COLD SPRING HARBOR LABORATORY PRESS, NEW YORK, vol. 12, no. 9, 1 May 1998 (1998-05-01), pages 1260-1268.
- D4: BRANDSTROM, H. (1) ET AL: 'Polymorphism in the promoter region of the human gene for osteoprotegerin: Correlation with bone mineral density.' JOURNAL OF BONE AND MINERAL RESEARCH, (SEPT., 1999) VOL. 14, NO. SUPPL. 1 PP. S334. MEETING INFO.: TWENTY-FIRST ANNUAL MEETING OF THE AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH ST. LOUIS, MISSOURI, USA SEPTEMBER 30-OCTOBER 4 1999 AMERICAN SOCIETY-

**SECTION I**

1. Sequence listing pages 52-55 filed with the letter of 27.03.2000 do not form part of the application (Rule 13ter.1(f) PCT).

**SECTION III**

2. For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT contracting states. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in a medical treatment and the use of such compound for the manufacture of a medicament for new medical treatment.

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In the above mentioned context the passage in claims 23, 24 "A method of ...therapy...and administering a medicament to the individual to prevent or treat..." is considered to cover treatment by therapy.

Therefore, claims 23, 24 relate to the subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**SECTION V**

**3. Novelty (Article 33(2) PCT)**

**3.1 The subject matter of claim 16 is not novel.**

Claim 16, relating to an oligonucleotide primer for use in amplification of the promoter region, is anticipated by D1. D1 (page 22, left column last paragraph to right column, first paragraph) discloses the construction of mutations in the promoter region of bone sialoprotein by the use of PCR and primers.

**3.2 The subject matter of claims 1-15 and 17 to 24 is novel.**

Claim 1, relating to a method of assessing a calcification condition status by the determination of the genotype of specified promoters, is not disclosed in the prior art documents.

Claims 17 to 22, relating to genes containing specified point mutations in the promoter region, are not disclosed in the prior art documents.

**3.3 Claims 23 and 24, relating to methods of therapy including the determination of predisposition according to method claims 1 to 15, are not disclosed in the prior art documents.**

**4. Inventive Step (Article 33(3) PCT)**

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International application No. PCT/EP00/00319

- 4.1 The subject matter of claims 1-3, 14, 15, 23 and 24 does not involve an inventive step.

D2 is considered to be the closest prior art. D2 (abstract) describes that mutations in the human matrix Gla gene are responsible for Keutel syndrome, i.e. an autosomal recessive disorder characterized by abnormal cartilage calcification, and this confirms its role in the regulation of extracellular matrix calcification.

D1 (abstract) describes that mutations in the promoter region of sialoprotein, a prominent component of the mineralized bone matrix, alters its expression and on page 219 (left column, last paragraph) the use of the osteopontin gene as osteoblastic marker is disclosed.

D3 (abstract) discloses the osteoprotegerin as an important component in the regulation of bone metabolism.

Claim 1 differs from D2 in that claim 1 relates to a method of assessing an individuals predisposition to a selected calcification condition status by determining the genotypes of promoters of the sialoprotein gene, the matrix gla protein gene, osteopontin gene, osteoprotegerin gene.

The technical problem would appear to reside in finding applications based on the teaching that mutations in genes involved in bone metabolism create disorders.

The skilled person, equipped with the knowledge of D2, would need no inventive skill to arrive at the subject matter of claim 1, since D2 teaches that mutations in the MGP open reading frame which alter the expression of the native protein influences extracellular matrix calcification. It is considered as general knowledge that the level of expression can be influenced, beside mutations in the open reading frames, also by mutations in the promoter region, i.e. a region that controls the expression. This is shown for example in D1, which document discloses that mutations in the promoter region of the sialoprotein gene influences its expression. Also the osteopontin gene and the osteoprotegerin gene are known to be important in the regulation of bone metabolism (see D1 and D3).

Dependent claims 2, 3, 14 and 15 do not contain any features which, in combination with the features of claim 1 to which they refer, meet the requirements of the PCT in respect of inventive step, since the mentioned features are merely alternatives from which the skilled person would choose, without resulting in any unexpected effect whatsoever.

Claims 23 and 24 relate to methods of therapy for osteoporosis (claim 23) or atherosclerosis (claim 24) by administering a medicament to the individual to prevent or treat or delay the onset if the individual is predisposed (according the method claims 1-15) with a not normal bone metabolism. Claims 23 and 24 do not contain any additional features which meet the requirements of the PCT in respect of inventive step, since it is obvious for the skilled person to carry out a method of therapy by administering a medicament after the assessment of an individuals predisposition has been carried out.

**4.2 Claims 4-13 and 17-22 would appear to involve an inventive step.**

D2 is considered to be the closest prior art (see item 4.1). Claims 4-13 and 17-22 differ from D2 that they refer to methods (claims 4-13) in which specific point mutations are identified to assess an individuals predisposition to a selected calcification condition status and the DNA sequences containing these mutations (claims 17-22).

The skilled person, equipped with the knowledge of D2, would not be able to arrive at the subject matter of these claims, since the prior art does not suggest that these point mutations would be involved in the expression level of the concerned markers involved in bone metabolism.

**4.3 The priority of the present application is validly claimed. Therefore, D4 does not belong to the state of the art as defined in Rule 64.1 PCT.**

**SECTION VII**

**5. The numbering of Figures 2-13 is not present on the drawings (Rule 11.13(e) PCT).**

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6. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 to D3 is not mentioned in the description, nor are these documents identified therein.

**SECTION VIII**

7. The back reference of "claims 1 to 22" in present claims 23 and 24 does not meet the requirements of clarity, since claims 16 to 22 do not determine a method of predisposition (Article 6 PCT).
8. With reference to page 8 (third paragraph) of the description, base number 1825 of the published osteopontin sequence (page 6, line 22) represents a thymine. This is supposed to be the wildtype sequence and consequently cytosine at this position would represent a mutation. In this respect the passage "and thymine at position 1825 is associated with a lower bone mass" is not clear (Article 6 PCT).

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PJS/P7850W0</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 00/00319</b>	International filing date (day/month/year) <b>17/01/2000</b>	(Earliest) Priority Date (day/month/year) <b>18/01/1999</b>
Applicant <b>OSTEOMETER BIOTECH A/S</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

**GENETIC PREDISPOSITION TO ABNORMAL CALCIFICATION CONDITIONS**

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.